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(21) International Application Number: PCT/US00/04830 (22) International Filing Date: 25 February 2000 (25.02.00) (30) Priority Data: 60/121,850 26 February 1999 (26.02.99) US (71) Applicant (for all designated States except US): EMISPHERE TECHNOLOGIES, INC. [US/US]; 765 Old Saw Mill River Road, Tarrytown, NY 10591 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): TANG, Pingwah [US/US]; 6 Beaver Hill Road, Elmsford, NY 10523 (US). LEONE-BAY, Andrea [US/US]; 20 Woodland Way, Ridgefield, CT 06877 (US). GSCHNEIDNER, David [US/US]; 44 Cerretta Street, Stamford, CT 06907 (US). (74) Agents: LESSLER, Jay, P. et al.; Darby & Darby P.C., 805 Third Avenue, New York, NY 10022-7513 (US).		(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, EE, ES, FI, GB, GD, GE, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: COMPOUNDS AND COMPOSITIONS FOR DELIVERING ACTIVE AGENTS (57) Abstract Compounds and compositions for the delivery of active agents are provided. Methods of administration and preparation are provided as well.		

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COMPOUNDS AND COMPOSITIONS FOR DELIVERING ACTIVE AGENTS

10 **FIELD OF THE INVENTION**

The present invention relates to compounds for delivering active agents, such as biologically or chemically active agents, to a target. These compounds are well suited for forming non-covalent mixtures with active agents for oral or intracolonic or other routes of administration to animals. Methods for the preparation and administration of such
15 compositions are also disclosed.

BACKGROUND OF THE INVENTION

Conventional means for delivering active agents are often severely limited by biological, chemical, and physical barriers. Typically, these barriers are imposed by the
20 environment through which delivery occurs, the environment of the target for delivery, and/or the target itself. Biologically and chemically active agents are particularly vulnerable to such barriers.

In the delivery to animals of biologically active and chemically active pharmacological and therapeutic agents, barriers are imposed by the body. Examples of
25 physical barriers are the skin, lipid bi-layers and various organ membranes that are relatively impermeable to certain active agents but must be traversed before reaching a target, such as the circulatory system. Chemical barriers include, but are not limited to, pH variations in the gastrointestinal (GI) tract and degrading enzymes.

These barriers are of particular significance in the design of oral delivery systems. Oral delivery of many biologically or chemically active agents would be the route of choice for administration to animals if not for biological, chemical, and physical barriers. Among the numerous agents which are not typically amenable to oral administration are

5 biologically or chemically active peptides, such as calcitonin and insulin; polysaccharides, and in particular mucopolysaccharides including, but not limited to, heparin; heparinoids; antibiotics; and other organic substances. These agents may be rapidly rendered ineffective or destroyed in the gastro-intestinal tract by acid hydrolysis, enzymes, and the like. In addition, the size and structure of macromolecular drugs may prohibit absorption.

10 Earlier methods for orally administering vulnerable pharmacological agents have relied on the co-administration of adjuvants (e.g., resorcinols and non-ionic surfactants such as polyoxyethylene oleyl ether and n-hexadecylpolyethylene ether) to increase artificially the permeability of the intestinal walls, as well as the co-administration of enzymatic inhibitors (e.g., pancreatic trypsin inhibitors, diisopropylfluorophosphate (DFF)

15 and trasylol) to inhibit enzymatic degradation. Liposomes have also been described as drug delivery systems for insulin and heparin. However, broad spectrum use of such drug delivery systems is precluded because: (1) the systems require toxic amounts of adjuvants or inhibitors; (2) suitable low molecular weight cargos, i.e. active agents, are not available; (3) the systems exhibit poor stability and inadequate shelf life; (4) the systems are difficult

20 to manufacture; (5) the systems fail to protect the active agent (cargo); (6) the systems adversely alter the active agent; or (7) the systems fail to allow or promote absorption of the active agent.

More recently, proteinoid microspheres have been used to deliver pharmaceuticals. For example, see US 5,401,516, US 5,443,841 and US RE35,862. In addition, certain

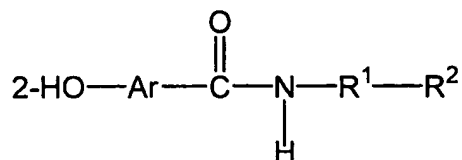
25 modified amino acids have been used to deliver pharmaceuticals. See, e.g., US 5,629,020; US 5,643,957; US 5,766,633; US 5,776,888; and US 5,866,536.

However, there is still a need for simple, inexpensive delivery systems which are easily prepared and which can deliver a broad range of active agents by various routes.

SUMMARY OF THE INVENTION

Compounds and compositions that are useful in the delivery of active agents are provided. The present invention encompasses compounds having the following formula, or salts thereof, or mixtures thereof.

5

**Compound A**

10 wherein

Ar is phenyl or naphthyl;

Ar is optionally substituted with C₁-C₄ alkyl, C₁-C₄ alkoxy, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl, aryloxy, a heterocyclic ring, C₅-C₇ carbocyclic ring, halogen, -OH, -SH, -CO₂R⁶, -NR⁷R⁸ or -N⁺R⁷R⁸R⁹Y⁻;

15 (a) R¹ is C₁-C₁₆ alkylene, C₂-C₁₆ alkenylene, C₂-C₁₆ alkynylene, C₆-C₁₆ arylene, (C₁-C₁₆ alkyl)arylene, or aryl(C₁-C₁₆ alkylene);

R² is -NR³R⁴ or -N⁺R³R⁴R⁵Y⁻;

R³ and R⁴ are independently hydrogen; oxygen; hydroxy; substituted or unsubstituted C₁-C₁₆ alkyl; substituted or unsubstituted C₂-C₁₆ alkenyl; substituted or unsubstituted C₂-C₁₆ alkynyl; substituted or unsubstituted aryl; substituted or unsubstituted alkylcarbonyl; substituted or unsubstituted arylcarbonyl; substituted or unsubstituted alkanesulfinyl; substituted or unsubstituted arylsulfinyl; substituted or unsubstituted alkanesulfonyl; substituted or unsubstituted arylsulfonyl; substituted or unsubstituted alkoxycarbonyl; or substituted or unsubstituted aryloxycarbonyl; and

25 R⁵ are independently hydrogen; substituted or unsubstituted C₁-C₁₆ alkyl; substituted or unsubstituted C₂-C₁₆ alkenyl; substituted or unsubstituted C₂-C₁₆ alkynyl; substituted or unsubstituted aryl; substituted or unsubstituted alkylcarbonyl; substituted or unsubstituted arylcarbonyl; substituted or unsubstituted alkanesulfinyl; substituted or unsubstituted arylsulfinyl; substituted or unsubstituted alkanesulfonyl; substituted or unsubstituted arylsulfonyl; substituted or unsubstituted alkoxycarbonyl; or substituted or unsubstituted aryloxycarbonyl;

30 (b) R¹, R², and R⁵ are as defined above; and

R^3 and R^4 are combined to form a 5, 6, or 7-membered heterocyclic ring or 5, 6 or 7-membered heterocyclic ring substituted with C_1 - C_6 alkyl, C_1 - C_6 alkoxy, aryl, aryloxy, oxo group, or carbocyclic ring; or

(c) R^2 and R^5 are as defined above;

5 R^1 and R^3 are combined to form a 5, 6, or 7-membered heterocyclic ring; or 5, 6, or 7-membered heterocyclic ring substituted with C_1 - C_6 alkyl, alkoxy, aryl, aryloxy, oxo group or carbocyclic ring; and

R^4 is hydrogen; oxygen; hydroxy; substituted or unsubstituted C_1 - C_{16} alkyl; substituted or unsubstituted C_2 - C_{16} alkenyl; substituted or unsubstituted C_2 - C_{16} alkynyl; 10 substituted or unsubstituted aryl; substituted or unsubstituted alkylcarbonyl; substituted or unsubstituted arylcarbonyl; substituted or unsubstituted alkanesulfinyl; substituted or unsubstituted arylsulfinyl; substituted or unsubstituted alkanesulfonyl; substituted or unsubstituted arylsulfonyl; substituted or unsubstituted alkoxycarbonyl; or substituted or unsubstituted aryloxycarbonyl;

15 R^6 is hydrogen; C_1 - C_4 alkyl; C_1 - C_4 alkyl substituted halogen or -OH; C_2 - C_4 alkenyl; or C_2 - C_4 alkenyl substituted with halogen or -OH;

R^7 , R^8 and R^9 are independently hydrogen; oxygen; C_1 - C_4 alkyl; C_1 - C_4 alkyl substituted with halogen or -OH; C_2 - C_4 alkenyl; or C_2 - C_4 alkenyl substituted with halogen or -OH; and

20 Y^- is halogen, hydroxide, sulfate, nitrate, phosphate, alkoxy, perchlorate, tetrafluoroborate, or carboxylate. An example of a suitable carboxylate includes, but is not limited to acetate.

Preferably, at least one of R^3 and R^4 is not hydrogen.

In a preferred embodiment, Ar is phenyl optionally substituted with methyl; 25 methoxy; hydroxy; or halogen. More preferably, Ar is unsubstituted phenyl or phenyl substituted with chlorine, more preferably at the 5 position.

According to another embodiment, R^1 is a C_1 - C_{12} substituted or unsubstituted alkylene. Preferably, R^1 is a C_3 - C_8 unsubstituted alkylene. More preferably, R^1 is a C_6 unsubstituted alkylene.

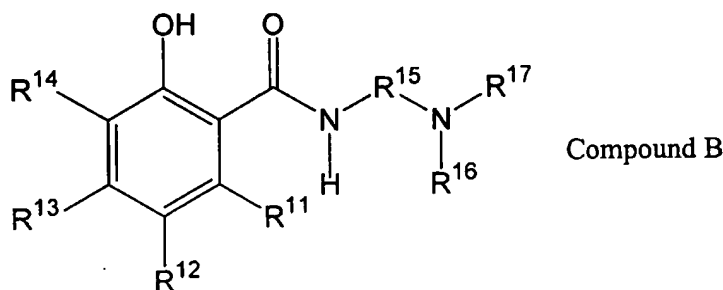
30 According to another embodiment, R^2 is $-NR^3R^4$; and (i) R^3 is phenyl or cyclohexyl and R^4 is hydrogen; (ii) R^3 and R^4 are both methyl; or (iii) R^3 and R^4 are combined to form

a 5- or 6-membered heterocyclic ring containing nitrogen, such as preferably pyrrolidinone, morpholine and imidazole.

According to yet another embodiment, R^2 is $-N^+R^3R^4R^5Y^-$.

According to a preferred embodiment, the compound has the formula:

5



10

wherein

R^{11} , R^{12} , R^{13} and R^{14} are independently hydrogen, -OH, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, or C_1 - C_4 haloalkoxy;

R^{15} is substituted or unsubstituted C_1 - C_{12} alkylene;

15

R^{16} and R^{17} are independently hydrogen, C_1 - C_4 alkyl, C_5 - C_7 cycloalkyl, or phenyl; or

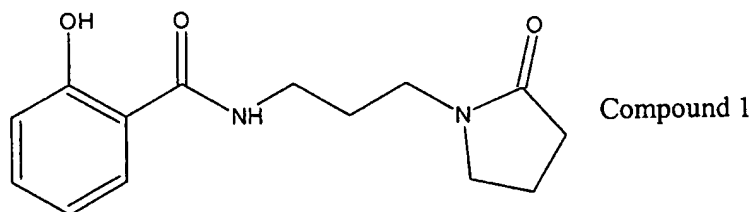
R^{16} and R^{17} are combined to form a 5 or 6 atom heterocyclic ring;

and salts thereof. Preferably, R^{11} , R^{12} , R^{13} and R^{14} are independently hydrogen; -OH; or halogen, more preferably chlorine. Preferably, R^{15} is unsubstituted C_3 - C_8 alkylene.

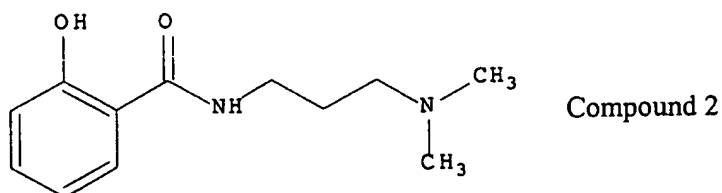
According to one embodiment, R^{16} and R^{17} are methyl. According to another
embodiment, R^{16} and R^{17} are combined to form a pyrrolidinone, morpholine, or imidazole
ring.

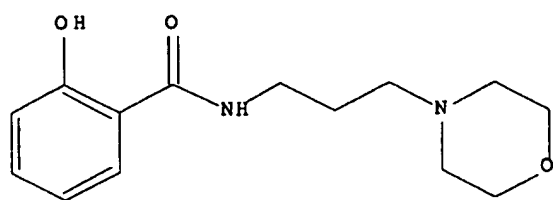
Preferred compounds of the present invention include, but are not limited to:

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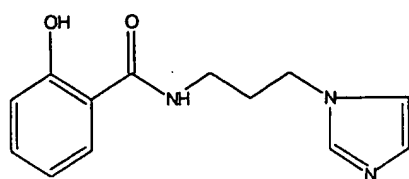
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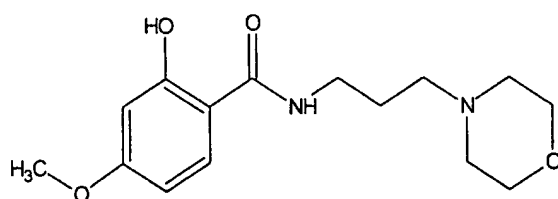
Compound 3

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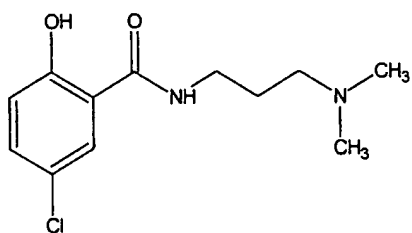
Compound 4

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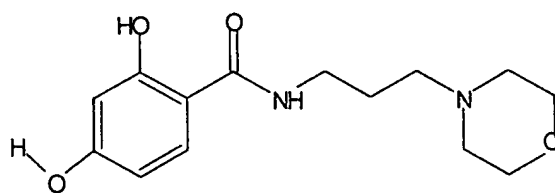
Compound 5

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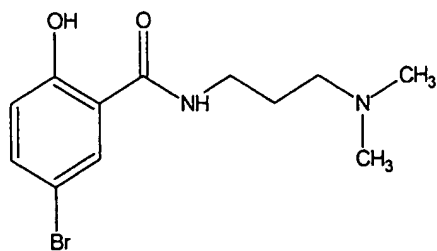
Compound 6

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Compound 7

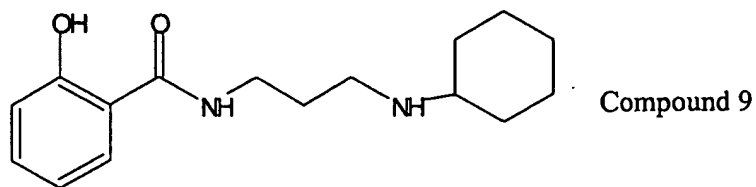
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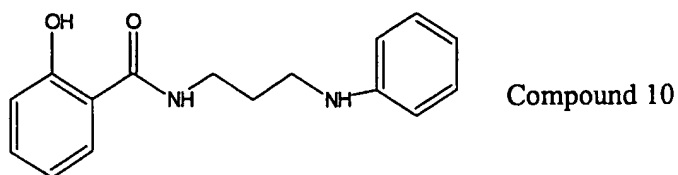
Compound 8

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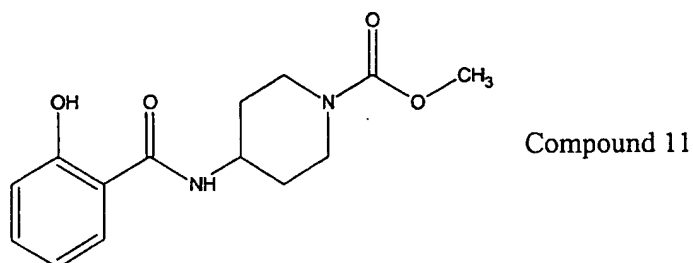
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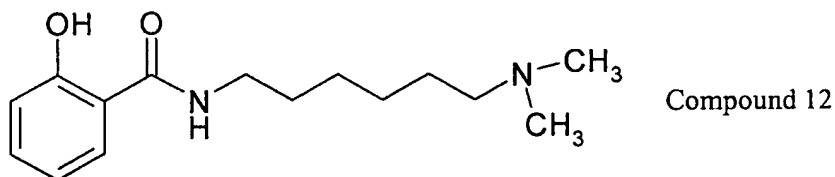
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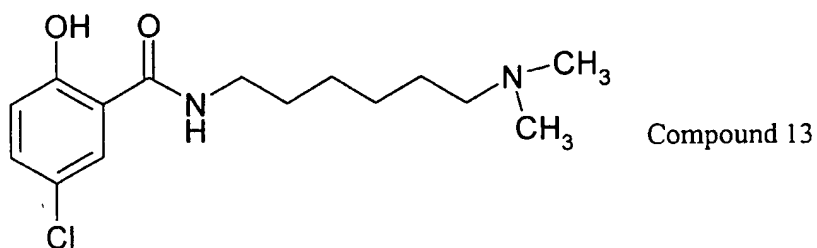
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25 The compositions of the present invention comprise at least one active agent, preferably a biologically or chemically active agent, and at least one of the compounds, or salts thereof, of the present invention. Methods for the preparation and administration of such compositions are also provided.

Also provided are dosage unit forms comprising the compositions. The dosing
30 vehicle can be a solid (such as a tablet, powder, or capsule) or a liquid.

Methods for administering a biologically active agent to an animal in need of the agent, especially by the oral or intracolonic routes, with the compositions of the present invention, are also provided.

5 DETAILED DESCRIPTION OF THE INVENTION

The term "substituted" as used herein includes, but is not limited to, the following substituents: halogen and -OH.

All carbon containing substituents described in the formulae for compounds A and B, such as alkyl, alkenyl, alkynyl moieties, may be linear or branched.

10 The compounds may be in the form of the amine salts. Salts include, but are not limited to, organic and inorganic salts, for example, ammonium salts and hydrochloride salts.

In general, the amine compounds of the present invention, *i.e.*, where R^2 is $-NR^3R^4$, may be prepared by reacting the appropriate O-acetyl salicyloyl chloride with the appropriate amine in the presence of a base, such as triethylamine. To obtain the
15 corresponding quaternary ammonium salt where R^2 is $-NHR^3R^4$, the amine compound is reacted with hydrochloric acid and preferably an excess of hydrochloric acid. To obtain the corresponding quaternary ammonium salt where R^2 is $-NR^3R^4R^5$ (where R^3 , R^4 , and R^5 are not hydrogen), the amine moiety of the amine compound is alkylated by methods
20 known in the art.

The compound may be purified by recrystallization or by fractionation on one or more solid chromatographic supports, alone or linked in tandem. Suitable recrystallization solvent systems include, but are not limited to, acetonitrile, methanol, and tetrahydrofuran. Fractionation may be performed on a suitable chromatographic support such as alumina,
25 using methanol/n-propanol mixtures as the mobile phase; reverse phase chromatography using trifluoroacetic acid/acetonitrile mixtures as the mobile phase; and ion exchange chromatography using water or an appropriate buffer as the mobile phase. When anion exchange chromatography is performed, preferably a 0-500 mM sodium chloride gradient is employed.

30

Active Agents

Active agents suitable for use in the present invention include biologically active agents and chemically active agents, including, but not limited to, pesticides, pharmacological agents, and therapeutic agents.

5 For example, biologically or chemically active agents suitable for use in the present invention include, but are not limited to, proteins; polypeptides; peptides; hormones; polysaccharides, and particularly mixtures of muco-polysaccharides; carbohydrates; lipids; other organic compounds; and particularly compounds which by themselves do not pass (or which pass only a fraction of the administered dose) through
10 the gastro-intestinal mucosa and/or are susceptible to chemical cleavage by acids and enzymes in the gastro-intestinal tract; or any combination thereof.

Further examples include, but are not limited to, the following, including synthetic, natural or recombinant sources thereof: growth hormones, including human growth hormones (hGH), recombinant human growth hormones (rhGH), bovine growth
15 hormones, and porcine growth hormones; growth hormone-releasing hormones; interferons, including α , β and γ ; interleukin-1; interleukin-2; insulin, including porcine, bovine, human, and human recombinant, optionally having counter ions including sodium, zinc, calcium and ammonium; insulin-like growth factor, including IGF-1; heparin, including unfractionated heparin, heparinoids, dermatans, chondroitins, low molecular
20 weight heparin, very low molecular weight heparin and ultra low molecular weight heparin; calcitonin, including salmon, eel and human; erythropoietin; atrial natriuretic factor; antigens; monoclonal antibodies; somatostatin; protease inhibitors; adrenocorticotropin, gonadotropin releasing hormone; oxytocin; leutinizing-hormone-releasing-hormone; follicle stimulating hormone; glucocerebrosidase; thrombopoietin;
25 filgrastim; prostaglandins; cyclosporin; vasopressin; cromolyn sodium (sodium or disodium chromoglycate); vancomycin; desferrioxamine (DFO); parathyroid hormone (PTH), including its fragments; antimicrobials, including anti-fungal agents; vitamins; analogs, fragments, mimetics or polyethylene glycol (PEG)-modified derivatives of these compounds; or any combination thereof.

Delivery systems

The compositions of the present invention comprise a delivery agent and one or more active agents. In one embodiment, one or more of the delivery agent compounds, or salts of these compounds, may be used as a delivery agent by mixing with the active agent
5 prior to administration.

The administration compositions may be in the form of a liquid. The solution medium may be water (for example, for salmon calcitonin, parathyroid hormone, and erythropoietin), 25% aqueous propylene glycol (for example, for heparin) and phosphate buffer (for example, for rhGH). Other dosing vehicles include polyethylene glycols,
10 sorbitol, maltitol, and sucrose. Dosing solutions may be prepared by mixing a solution of the delivery agent compound with a solution of the active agent, just prior to administration. Alternately, a solution of the delivery agent (or active agent) may be mixed with the solid form of the active agent (or delivery agent). The delivery agent compound and the active agent may also be mixed as dry powders. The delivery agent
15 compound and the active agent can also be admixed during the manufacturing process.

The dosing solutions may optionally contain additives such as phosphate buffer salts, citric acid, glycols, or other dispersing agents. Stabilizing additives may be incorporated into the solution, preferably at a concentration ranging between about 0.1 and 20% (w/v).

20 The administration compositions may alternately be in the form of a solid, such as a tablet, capsule or powder. Solid dosage forms may be prepared by mixing the solid form of the compound with the solid form of the active agent. Alternately, a solid may be obtained from a solution of compound and active agent by methods known in the art, such as freeze drying, precipitation, crystallization and solid dispersion.

25 The administration compositions of the present invention may also include one or more enzyme inhibitors. Such enzyme inhibitors include, but are not limited to, compounds such as actinonin or epiactinonin and derivatives thereof. Other enzyme inhibitors include, but are not limited to, aprotinin (Trasylol) and Bowman-Birk inhibitor.

The amount of active agent used in an administration composition of the present
30 invention is an amount effective to accomplish the purpose of the particular active agent for the target indication. The amount of active agent in the compositions typically is a pharmacologically, biologically, therapeutically, or chemically effective amount.

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However, the amount can be less than that amount when the composition is used in a dosage unit form because the dosage unit form may contain a plurality of compound/active agent compositions or may contain a divided pharmacologically, biologically, therapeutically, or chemically effective amount. The total effective amount can then be
5 administered in cumulative units containing, in total, an effective amount of the active agent.

The total amount of active agent to be used can be determined by methods known to those skilled in the art. However, because the compositions may deliver active agents more efficiently than prior compositions, lower amounts of biologically or chemically
10 active agents than those used in prior dosage unit forms or delivery systems can be administered to the subject, while still achieving the same blood levels and/or therapeutic effects.

The presently disclosed compounds deliver biologically and chemically active agents, particularly in oral, intranasal, sublingual, intraduodenal, subcutaneous, buccal,
15 intracolonic, rectal, vaginal, mucosal, pulmonary, transdermal, intradermal, parenteral, intravenous, intramuscular and ocular systems, as well as traversing the blood-brain barrier.

Dosage unit forms can also include any one or combination of excipients, diluents, disintegrants, lubricants, plasticizers, colorants, flavorants, taste-masking agents, sugars,
20 sweeteners, salts, and dosing vehicles, including, but not limited to, water, 1,2-propane diol, ethanol, olive oil, or any combination thereof.

The compounds and compositions of the subject invention are useful for administering biologically or chemically active agents to any animals, including but not limited to birds such as chickens; mammals, such as rodents, cows, pigs, dogs, cats,
25 primates, and particularly humans; and insects.

The system is particularly advantageous for delivering chemically or biologically active agents that would otherwise be destroyed or rendered less effective by conditions encountered before the active agent reaches its target zone (i.e. the area in which the active agent of the delivery composition is to be released) and within the body of the animal to
30 which they are administered. Particularly, the compounds and compositions of the present invention are useful in orally administering active agents, especially those that are not ordinarily orally deliverable, or those for which improved delivery is desired.

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The compositions comprising the compounds and active agents have utility in the delivery of active agents to selected biological systems and in an increased or improved bioavailability of the active agent compared to administration of the active agent without the delivery agent. Delivery can be improved by delivering more active agent over a
5 period of time, or in delivering active agent in a particular time period (such as to effect quicker or delayed delivery) or over a period of time (such as sustained delivery).

Following administration, the active agent present in the composition or dosage unit form is taken up into the circulation. The bioavailability of the agent is readily assessed by measuring a known pharmacological activity in blood, e.g. an increase in
10 blood clotting time caused by heparin, or a decrease in circulating calcium levels caused by calcitonin. Alternately, the circulating levels of the active agent itself can be measured directly.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

15 The following examples illustrate the invention without limitation. All parts are given by weight unless otherwise indicated.

Example 1

Preparation of Compound 1

20 To a 250 ml three neck round-bottomed flask equipped with a magnetic stirrer and a reflux condenser was placed 7.11 g (50 mmol) of 1-(3-aminopropyl)-2-pyrrolidinone in 70 ml of dichloromethane. Chlorotrimethylsilane (6.34 ml, 50 mmol) was added in one portion. The mixture was refluxed for about 1 hour. The reaction was cooled to approximately 5° C. Triethylamine (10.45 ml, 75 mmol) was added dropwise, followed
25 by the addition dropwise of a solution of 9.93 g (50 mmol) of o-acetylsalicyloyl chloride in 20 ml of dichloromethane. After the addition had been completed, the mixture was allowed to warm to room temperature and was stirred for an additional hour. The mixture was concentrated *in vacuo* to an oil. An ice cold solution of 2M sodium hydroxide (100 ml, 200 mmol) was added and the mixture was stirred for about 2 hours. The basic
30 solution was acidified with a 10% solution of hydrochloric acid. The organic product was extracted with ethyl acetate. The organic phase was washed with water until neutrality, dried and concentrated *in vacuo* to afford a residue which was purified by flash column

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chromatograph to yield 7.9 g (61%) of a white solid. Spectroscopic data and combustion analysis indicated the assigned structure.

Compound 2 was also prepared by this method. Compounds 3-11 may also be prepared by this method.

5

Preparation of Compound 12

A slurry of 18.02 g (110 mmol) of carsalam, 18.0 ml (15.84 g, 109 mmol) of 6-dimethylamino-1-hexanol, 29.12 g (111 mmol) of triphenylphosphine, and 150 ml of tetrahydrofuran was treated with a solution of 21.8 ml (22.39 g, 111 mmol) of disopropyl azodicarboxylate and 40 ml of tetrahydrofuran, added dropwise over 20 minutes, causing the temperature of the slurry to rise to about 67° C. The reaction mixture was allowed to cool back to about 25° C and stir for about 20 hours. The solution was treated with 150 ml (300 mmol) of aqueous 2N sodium hydroxide and warmed to about 60° C for about 90 minutes. The reaction mixture was washed with ethyl acetate (2 x 60 ml). The aqueous phase was acidified with 4% aqueous hydrochloric acid to a pH slightly less than about 0 and washed with ethyl acetate (2 x 60 ml). The pH of the aqueous phase was raised to about 4.5 with 50% aqueous potassium carbonate and washed with ethyl acetate (2 x 60 ml). The aqueous phase was treated with solid sodium bicarbonate and extracted with ethyl acetate (14 x 60 ml). The combined 14 ethyl acetate extracts were dried over sodium sulfate and concentrated to a viscous liquid. The liquid was taken up into a minimum amount of ethyl acetate, diluted with 100 ml of hexanes and treated in an ice bath with 150 ml of hexanes, causing a white solid to develop. A total of 13.65 g of N-(6-dimethylaminohexyl)salicylamide was isolated by filtration.

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Preparation of Compound 13

A slurry of 5.79 g (29.3 mmol) of 6-chlorocarsalam, 4.80 ml (4.22 g, 29.1 mmol) of 6-dimethylamino-1-hexanol, 7.71 g (29.4mmol) of triphenylphosphine, and 50 ml of tetrahydrofuran was treated with a solution of 5.8 ml (5.96 g, 29.5 mmol) of disopropyl azodicarboxylate and 20 ml of tetrahydrofuran, added dropwise over 20 minutes, causing the temperature of the slurry to rise to about 67° C. The reaction mixture was allowed to cool back to about 25° C and stir for about 20 hours. The solution was treated with 50 ml (100 mmol) of aqueous 2N sodium hydroxide and warmed to about 60° C for about 120

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minutes. The reaction mixture was washed with ethyl acetate (2 x 40 ml). The aqueous phase was acidified with 4% aqueous hydrochloric acid to a pH of about 1 and washed with ethyl acetate (2 x 40 ml). The pH of the aqueous phase was raised to about 5.5 with 50% aqueous potassium carbonate, causing a white solid to develop. A total of 5.25 g of

5 N-(6-dimethylaminohexyl)-5-chlorosalicylamide was isolated by filtration.

Example 2

Oral Delivery of Salmon Calcitonin (sCT)

10 Oral dosing (PO) compositions of delivery agent compound and salmon calcitonin (sCT) in water were prepared. Typically, 450 mg of compound was added to 2.0 ml of water. Either the sodium salt of the compound was used or the free acid was converted to the sodium salt by stirring the resultant solution and adding one equivalent of sodium hydroxide (1.0 N) and diluting with water. The solution was vortexed, then heated (about

15 37° C) and sonicated. The pH was adjusted to about 7 (6.5 to 8.5) with sodium hydroxide or hydrochloric acid. 90 mg sCT from a stock solution was added to the solution. Water was then added to bring the total volume to about 3.0 ml (varying depending on the solubility of the delivery agent compound) and vortexed. The final delivery agent compound dose, sCT dose, and volume dose amounts are listed below in Table 1.

20 The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250 g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. A dosing group of five rats was administered one of the dosing solutions. For oral dosing, an 11 cm Rusch 8 French catheter was adapted to a 1 ml syringe with a pipette tip. The syringe was filled

25 with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the incisors. Solution was administered by pressing the syringe plunger.

Blood samples were collected serially from the tail artery, typically before administration and 10, 20, 30, 60 and 90 minutes after administration. Serum sCT was

30 determined by testing with an EIA kit (Kit # EIAS-6003 from Peninsula Laboratories, Inc. of San Carlos, CA). Numbers were adjusted according to baseline values obtained prior to

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administration. The results from the five rats in each dosing group were averaged for each time point. The maximum is reported below in Table 1.

Table 1

5 Oral Delivery of Salmon Calcitonin (sCT)

Compound	Volume Dose (ml/kg)	Compound Dose (mg/kg)	sCT Dose (mg/kg)	Mean Peak Serum Sct (pg/ml \pm SD)(SE)
12	1	150	30	764 \pm 443 (167)

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Example 4Oral Delivery of Low Molecular Weight Heparin (LMWH)

Intracolonic (IC) compositions containing a delivery agent compound and low molecular weight heparin (LMWH) in 25% aqueous propylene glycol were prepared. Either the sodium salt of the compound was used or the free acid was converted to the sodium salt with one equivalent of sodium hydroxide. Typically, delivery agent compound and LMWH (91 IU/mg, average molecular weight about 5,000) were mixed by vortex as dry powders. This dry mixture was dissolved in 25% v/v aqueous propylene glycol, vortexed and placed in a sonicator (37° C). The pH was adjusted to about 7 (6.5-8.5) with 2N aqueous sodium hydroxide. The dosing solution was sonicated to produce a clear solution. The final volume was adjusted to 3.0 ml. The final delivery agent compound dose, LMWH dose, and volume dose amounts are listed below in Table 2.

The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 275-350 g were fasted for 24 hours and were anesthetized with ketamine hydrochloride (88 mg/kg) intramuscularly immediately prior to dosing. A dosing group of five rats was administered one of the dosing solutions. For intracolonic (IC) dosing, a 7.5cm, 8 fr Rusch catheter was adapted to a 1 ml syringe with a pipette tip. The dosing catheter was inserted into the colon through the anus until the tube was no longer visible. The dosing solution was expressed slowly into the colon by pressing the syringe plunger.

Citrated blood samples were collected by cardiac puncture following the administration of ketamine (88 mg/kg), typically 0.5, 1.0, 2.0, 3.0 and 4.0 hours after administration.

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LMWH activity was determined using the anti-Factor Xa assay CHROMOSTRATE[®] heparin anti-X_a assay, available from Organon Teknika Corporation of Durham, NC. Baseline values are about zero IU/ml. Results from the five rats in each group were averaged for each time point. The mean peak plasma heparin concentration is reported below in Table 2.

Table 2

Intracolonic Delivery of LMWH

Compound	Method of Administration	Volume Dose (ml/kg)	Compound Dose (mg/kg)	LMWH Dose (IU/kg)	Mean Peak Plasma Heparin Concentration (IU/ml) \pm Standard Deviation
12	IC	1	50	750	0.13 \pm 0.05

Example 5Recombinant Human Growth Hormone (rhGH)

Oral gavage (PO) dosing solutions of delivery agent compound and rhGH in phosphate buffer were prepared. A solution of the compound was made either with the sodium salt of the compound or by converting the free acid to its sodium salt. Typically, a solution of the compound was prepared in phosphate buffer and stirred, adding one equivalent of sodium hydroxide (1.0 N) when making the sodium salt. The final dosing solutions were prepared by mixing the compound solution with an rhGH stock solution (15 mg rhGH/ml made by mixing as powders 15 mg rhGH, 75 mg D-mannitol, 15 mg glycine and 3.39 mg dibasic sodium phosphate, then diluting with 2% glycerol) and diluting to the desired volume (usually 3.0 ml). The compounds and rhGH dose amounts are listed below in Table 3.

The typical dosing and sampling protocols were as follows. Male Sprague-Dawley rats weighing between 200-250g were fasted for 24 hours and administered ketamine (44 mg/kg) and chlorpromazine (1.5 mg/kg) 15 minutes prior to dosing. A dosing group of five rats was administered one of the dosing solutions. For oral gavage (PO), an 11cm Rusch 8 French catheter was adapted to a 1 ml syringe with a pipette tip. The syringe was

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filled with dosing solution by drawing the solution through the catheter, which was then wiped dry. The catheter was placed down the esophagus leaving 1 cm of tubing past the rat's incisors. Solution was administered by pressing the syringe plunger.

Blood samples were collected serially from the tail artery, typically at time = 15, 30, and 45 minutes. The five samples from each time period were pooled. Serum rhGH concentrations were quantified by an rhGH immunoassay test kit (Kit # K1F4015 from Genzyme Corporation Inc., Cambridge, MA). Previous studies indicated baseline values of about zero.

The maximum concentration for each group and the area under the curve (AUC) are reported below in Table 3.

Table 3
Oral Delivery of rhGH in Rats

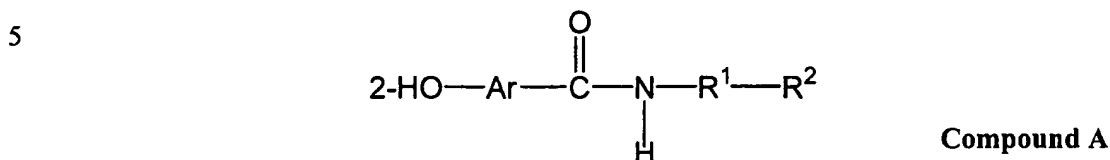
Compound	Method of Administration	Volume dose (ml/kg)	Compound Dose (mg/kg)	rhGH Dose (mg/kg)	Mean Peak Serum [rhGH] (ng/ml)	AUC
12	PO	1	200	3	51.76	1044.75

The above mentioned patents, applications, test methods, and publications are hereby incorporated by reference in their entirety.

Many variations of the present invention will suggest themselves to those skilled in the art in light of the above detailed description. All such obvious variations are within the fully intended scope of the appended claims.

WHAT IS CLAIMED IS:

1. A compound having the formula



wherein

- 10 Ar is phenyl or naphthyl;

Ar is optionally substituted with C₁-C₄ alkyl, C₁-C₄ alkoxy, C₂-C₄ alkenyl, C₂-C₄ alkynyl, aryl, aryloxy, a heterocyclic ring, C₅-C₇ carbocyclic ring, halogen, -OH, -SH, -CO₂R⁶, -NR⁷R⁸ or -N⁺R⁷R⁸R⁹Y⁻;

- (a) R¹ is C₁-C₁₆ alkylene, C₂-C₁₆ alkenylene, C₂-C₁₆ alkynylene, C₆-C₁₆ arylene, (C₁-C₁₆ alkyl)arylene, or aryl(C₁-C₁₆ alkylene);

R² is -NR³R⁴ or -N⁺R³R⁴R⁵Y⁻;

- R³ and R⁴ are independently hydrogen; oxygen; hydroxy; substituted or unsubstituted C₁-C₁₆ alkyl; substituted or unsubstituted C₂-C₁₆ alkenyl; substituted or unsubstituted C₂-C₁₆ alkynyl; substituted or unsubstituted aryl; substituted or unsubstituted alkylcarbonyl; substituted or unsubstituted arylcarbonyl; substituted or unsubstituted alkanesulfinyl; substituted or unsubstituted arylsulfinyl; substituted or unsubstituted alkanesulfonyl; substituted or unsubstituted arylsulfonyl; substituted or unsubstituted alkoxycarbonyl; or substituted or unsubstituted aryloxycarbonyl; and

- R⁵ are independently hydrogen; substituted or unsubstituted C₁-C₁₆ alkyl; substituted or unsubstituted C₂-C₁₆ alkenyl; substituted or unsubstituted C₂-C₁₆ alkynyl; substituted or unsubstituted aryl; substituted or unsubstituted alkylcarbonyl; substituted or unsubstituted arylcarbonyl; substituted or unsubstituted alkanesulfinyl; substituted or unsubstituted arylsulfinyl; substituted or unsubstituted alkanesulfonyl; substituted or unsubstituted arylsulfonyl; substituted or unsubstituted alkoxycarbonyl; or substituted or unsubstituted aryloxycarbonyl;

- (b) R¹, R², and R⁵ are as defined above; and

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R^3 and R^4 are combined to form a 5, 6, or 7-membered heterocyclic ring or 5, 6 or 7-membered heterocyclic ring substituted with C_1 - C_6 alkyl, C_1 - C_6 alkoxy, aryl, aryloxy, oxo group, or carbocyclic ring; or

(c) R^2 and R^5 are as defined above;

5 R^1 and R^3 are combined to form a 5, 6, or 7-membered heterocyclic ring; or 5, 6, or 7-membered heterocyclic ring substituted with C_1 - C_6 alkyl, alkoxy, aryl, aryloxy, oxo group or carbocyclic ring; and

R^4 is independently hydrogen; oxygen; hydroxy; substituted or unsubstituted C_1 - C_{16} alkyl; substituted or unsubstituted C_2 - C_{16} alkenyl; substituted or
10 unsubstituted C_2 - C_{16} alkynyl; substituted or unsubstituted aryl; substituted or unsubstituted alkylcarbonyl; substituted or unsubstituted arylcarbonyl; substituted or unsubstituted alkanesulfinyl; substituted or unsubstituted arylsulfinyl; substituted or unsubstituted alkanesulfonyl; substituted or unsubstituted arylsulfonyl; substituted or unsubstituted alkoxycarbonyl; or substituted or unsubstituted aryloxycarbonyl;

15 R^6 is hydrogen; C_1 - C_4 alkyl; C_1 - C_4 alkyl substituted halogen or -OH; C_2 - C_4 alkenyl; or C_2 - C_4 alkenyl substituted with halogen or -OH;

R^7 , R^8 and R^9 are independently hydrogen; oxygen; C_1 - C_4 alkyl; C_1 - C_4 alkyl substituted with halogen or -OH; C_2 - C_4 alkenyl; or C_2 - C_4 alkenyl substituted with halogen or -OH; and

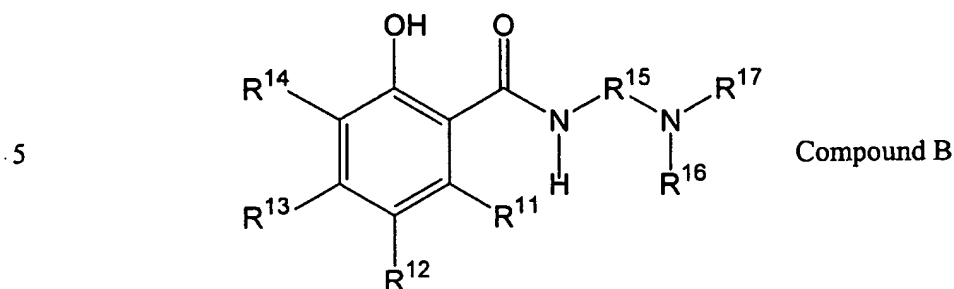
20 Y is halogen, hydroxide, sulfate, nitrate, phosphate, alkoxy, perchlorate, tetrafluoroborate, or carboxylate; or salt thereof.

2. The compound of claim 1, wherein Ar is phenyl or phenyl substituted with
25 methyl, methoxy, hydroxy, or halogen; and R^1 is a C_1 - C_{12} substituted or unsubstituted alkylene.

3. The compound of claim 1, wherein R^2 is $-NR^3R^4$.

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4. The compound of claim 1, wherein the compound has the formula:



wherein

- 10 R^{11} , R^{12} , R^{13} and R^{14} are independently hydrogen, -OH, halogen, C_1 - C_4 alkyl, C_1 - C_4 haloalkyl, C_1 - C_4 alkoxy, or C_1 - C_4 haloalkoxy;

R^{15} is substituted or unsubstituted C_1 - C_{12} alkyl; and

R^{16} and R^{17} are independently hydrogen, C_1 - C_4 alkyl, C_5 - C_7 cycloalkyl, or phenyl; or

R^{16} and R^{17} are combined to form a 5 or 6 atom heterocyclic ring;

or salt thereof.

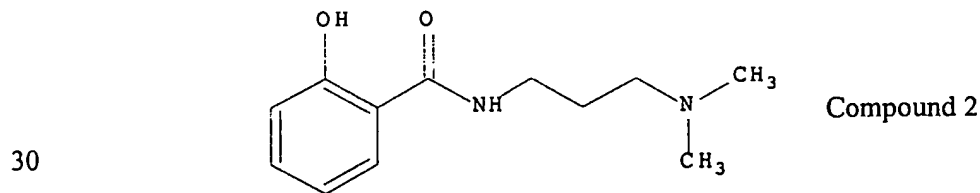
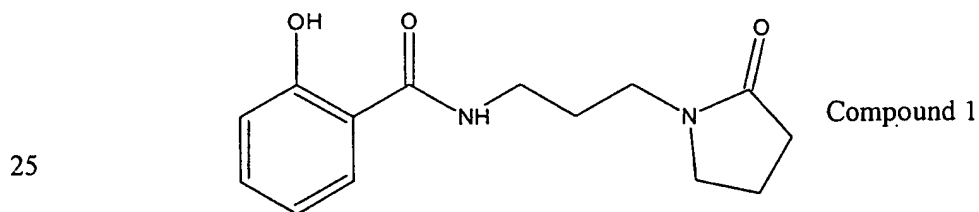
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5. The compound of claim 4, wherein R^{11} , R^{12} , R^{13} and R^{14} are independently hydrogen, -OH, or halogen; and R^{15} is unsubstituted C_3 - C_8 alkylene.

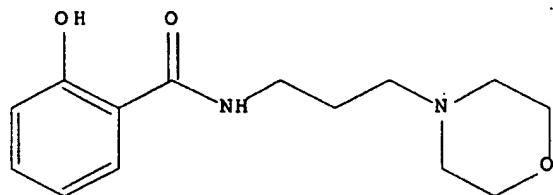
6. The compound of claim 4, wherein R^{16} and R^{17} are methyl.

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7. The compound of claim 1 selected from the group consisting of

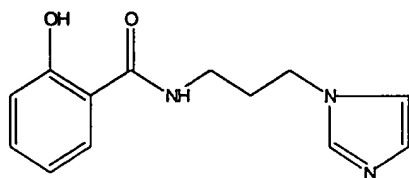


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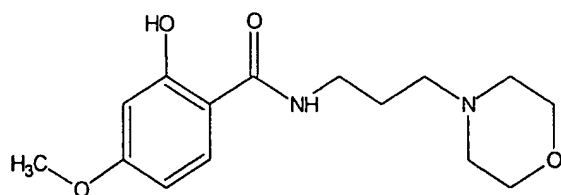
Compound 3

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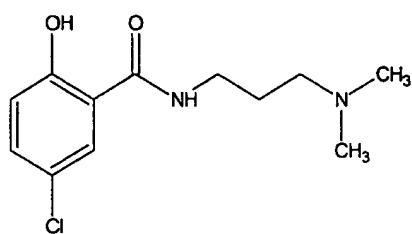
Compound 4

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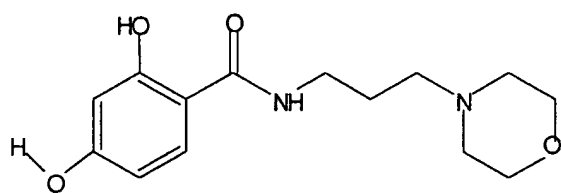
Compound 5

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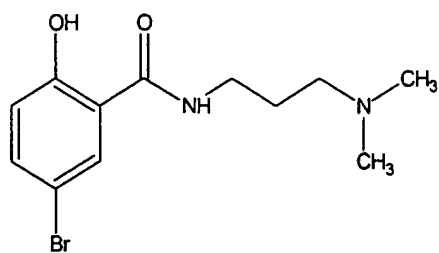
Compound 6

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Compound 7

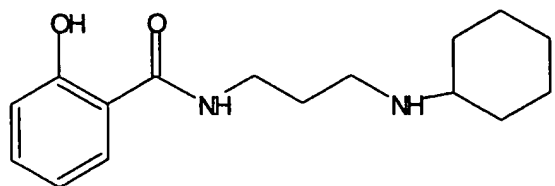
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Compound 8

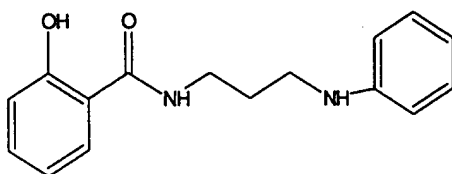
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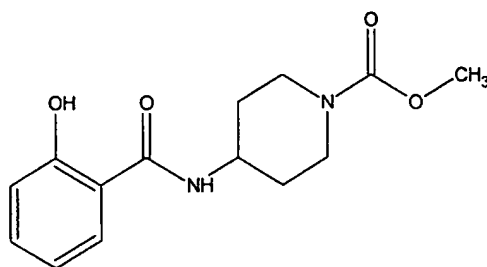
Compound 9

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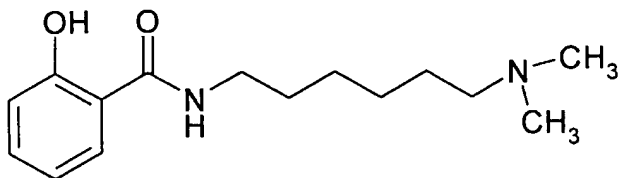
Compound 10

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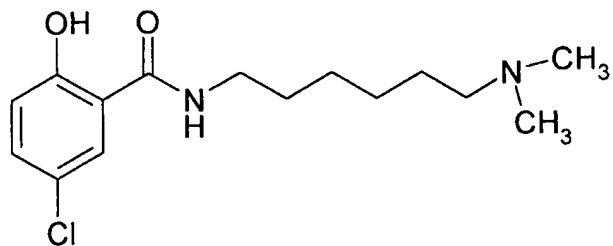
Compound 11

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Compound 12

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Compound 13

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and salts thereof.

8. A composition comprising

(A) an active agent; and

(B) at least one compound of claim 1.

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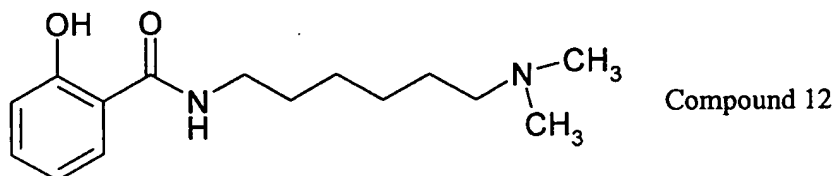
9. A composition comprising
(A) an active agent; and
(B) at least one compound of claim 4.
- 5 10. A composition comprising
(A) an active agent; and
(B) at least one compound of claim 7.
11. The composition of claim 10, wherein the active agent is selected from the
10 group consisting of a biologically active agent, a chemically active agent, and a combination thereof.
12. The composition of claim 11, wherein the biologically active agent comprises
at least one protein, polypeptide, peptide, hormone, polysaccharide, mucopolysaccharide,
15 carbohydrate, or lipid.
13. The composition of claim 11, wherein the biologically active agent is selected
from the group consisting of growth hormones, human growth hormones (hGH), recombinant
human growth hormones (rhGH), bovine growth hormones, porcine growth hormones, growth
20 hormone-releasing hormones, interferons, α -interferon, β -interferon, γ -interferon, interleukin-
1, interleukin-2, insulin, porcine insulin, bovine insulin, human insulin, human recombinant
insulin, insulin-like growth factor (IGF), IGF-1, heparin, unfractionated heparin, heparinoids,
dermatans, chondroitins, low molecular weight heparin, very low molecular weight heparin,
ultra low molecular weight heparin, calcitonin, salmon calcitonin, eel calcitonin, human
25 calcitonin; erythropoietin (EPO), atrial natriuretic factor, antigens, monoclonal antibodies,
somatostatin, protease inhibitors, adrenocorticotropic hormone, gonadotropin releasing hormone,
oxytocin, luteinizing-hormone-releasing-hormone, follicle stimulating hormone,
glucocerebrosidase, thrombopoietin, filgrastim, prostaglandins, cyclosporin, vasopressin,
cromolyn sodium, sodium chromoglycate, disodium chromoglycate, vancomycin,
30 desferrioxamine (DFO), parathyroid hormone (PTH), fragments of PTH, antimicrobials, anti-
fungal agents, vitamins; analogs, fragments, mimetics and polyethylene glycol (PEG)-
modified derivatives of these compounds; and any combination thereof.

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14. The composition of claim 13, wherein the biologically active agent comprises recombinant human growth hormone or salmon calcitonin.

15. The composition of claim 11, wherein the compound is

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10 or a salt thereof.

16. A dosage unit form comprising:

(A) the composition of claim 10; and

(B) (a) an excipient

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(b) a diluent,

(c) a disintegrant,

(d) a lubricant,

(e) a plasticizer,

(f) a colorant,

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(g) a dosing vehicle, or

(h) any combination thereof.

17. The dosage unit form of claim 16, wherein the dosage unit form is in the form of a tablet, a capsule, a powder, or a liquid.

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18. The dosage unit form of claim 16, wherein the dosing vehicle is liquid selected from the group consisting of water, 25% aqueous propylene glycol, phosphate buffer, 1,2-propane diol, ethanol, and any combination thereof.

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19. A method for administering a biologically-active agent to an animal in need of the agent, the method comprising administering orally to the animal the composition of claim 1.

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20. A method for administering a biologically-active agent to an animal in need of the agent, the method comprising administering orally to the animal the composition of claim 7.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US00/04830

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07C 233/00

US CL : 564/170, 171, 173

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 564/170, 171, 173

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

STN, CAS, FILE REGISTRY, STRUCTURE, FILE CA

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	DAVARAN et al., Release of 5-aminosalicylic Acid from Acrylic Type Polymeric Prodrugs Designed for Colon-specific Drug Delivery, Chem. Abstract No. 63362, Vol. 131, J. Controlled Release (1999) 58(3), pages 279-287.	1, 3-5, 8-13 ----- 2, 6, 7, 14-20
X --- Y	JOHANSEN et al., Pro-drugs as Drug Delivery Systems, Chem. Abstract No. 162641, Vol. 94, Int. J. Pharm. (1980), 7(2), pages 119-27.	1, 3-5, 8-13 ----- 2, 6, 7, 14-20

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:	*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
A document defining the general state of the art which is not considered to be of particular relevance	*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
E earlier document published on or after the international filing date	*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step, when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	*G* document member of the same patent family
O document referring to an oral disclosure, use, exhibition or other means	
P document published prior to the international filing date but later than the priority date claimed	

Date of the actual completion of the international search

19 MAY 2000

Date of mailing of the international search report

06 JUN 2000

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